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What is the effect of screening mammography on breast cancer incidence?

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The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."[1] The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS). The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

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Selected article

Bleyer A, Welch HG. Effect of 3 decades of screening mammography on breast-cancer incidence. *New Engl J Med* 2012;367:1998–2005.

Abstract

Objective: To determine if screening mammography produced the expected increase in the incidence of early-stage breast cancer and reduced the expected incidence of late-stage breast cancer in women 40 years of age or older. **Design:** Population-based observation study using a before and after cohort time series design. **Data Sources:** 1) National Health Interview Survey; 2) Surveillance, Epidemiology and End Results (SEER) data; 3) United States Census. **Results:** The introduction of screening mammography in the United States has been associated with a doubling in the number of cases of early-stage breast cancer detected each year from 112 to 234 cases per 100 000 women — an absolute increase of 122 cases per 100 000 women. Concomitantly, the rate at which women present with late-stage cancer has decreased from 102 to 94 cases per 100 000 women — an absolute decrease of 8 cases per 100 000 women. With the assumption of a constant underlying disease burden, it was estimated that only 8 of the 122 additional early-stage cancers diagnosed would progress to advanced disease. After excluding the transient excess incidence associated with hormone replacement therapy and adjusting for trends in the incidence of breast cancer among women younger than 40 years old, it was estimated that breast cancer was overdiagnosed (i.e., tumours were detected on screening that would never have led to clinical symptoms) in 70 000 women in 2008 and 1.3 million women in the past 30 years. **Conclusion:** Despite substantial increases in the number of early-stage breast cancer detected, screening mammography has only marginally reduced the rate at which women present with late-stage cancer.

Commentary

The efficacy of screening mammography has been established through randomized controlled trials and has been shown to reduce breast cancer mortality in some age groups. The principle of screening is to detect life-threatening disease at an earlier, more curable stage. Based on this logic, there is consensus that, in populations in whom screening is widespread, a decrease in the incidence of advanced breast cancer is the best indicator of the contribution of screening to decreasing breast cancer mortality.[1] Consistent with this concept, Bleyer and Welch[2] examined trends in breast cancer stage in the United States from 1976 to 2008 to determine if the introduction of screening mammography produced the expected reduction in incidence of late-stage breast cancer as well as the expected increase in the incidence of early-stage breast cancer in women aged 40 years or older.

The study is a population-based observational before and after cohort time series. By measuring outcomes at multiple points in time, an attempt can be made to determine whether the intervention (mammographic screening) at a particular point in time has had an effect significantly greater than any underlying trend. The main finding was that the introduction of screening mammography decreased late-stage cancer by only 8% from 102 to 94 cases per 100 000 women and was associated with a doubling in the number of cases of early-stage breast cancer detected each year, from 112 to 234 cases per 100 000 women. Based on this analysis it was estimated that breast cancer was overdiagnosed in 1.3 million women in the United States in the past 30 years and that 31% of all breast cancers found in 2008 represented an overdiagnosis — finding "disease" that will never cause symptoms or death during a patient's lifetime but leads to unnecessary and harmful treatments).

Data from the National Health Interview Survey[3] were used to assess trends in the proportion of women aged 40 years or older who underwent screening mammography. Data from the Surveillance Epidemiology and End Results[4] (SEER) database were used to assess trends between 1976 and 2008 in the incidence, stage and survival rates of women with breast cancer. Finally, annual estimates of the population of women aged 40 years or older were obtained from the United States Census. Using these data, the authors calculated the absolute change between 1976 and 1978 (the baseline rate) and between 2005 and 2008 in the incidence of early- and late-stage breast cancer in women older than 40 years. The authors also examined trends in the incidence of breast cancer over this time frame in women younger than 40 years who were assumed not to have undergone screening in case there were other changes that might have caused a change in incidence.

There are limitations to the study owing to the complexity of the analysis, assumptions made and the potential for confounding factors. Confounding occurs when the effect or association between an exposure and outcome is distorted by the presence of another unmeasured variable. A confounding factor can threaten the validity of the findings of a study. The authors tried to control for the decreased use of hormone replacement therapy that occurred after 2002 following the Women's Health Initiative report showing that the therapy increased the risk of breast cancer. This decrease in use has resulted in a subsequent measurable decrease in the incidence of breast cancer.[5]

In addition there are other potential confounding factors that were not considered, including the introduction of sentinel node biopsy, the increased use of staging investigations and the introduction of chemoprevention for breast cancer. Over the last 10–15 years, sentinel lymph node biopsy (SLNB) has replaced axillary node dissection as the diagnostic test for women with newly diagnosed breast cancers and clinically negative lymph nodes. Sentinel lymph node biopsy upstages women with node-positive breast cancer owing to a

more in-depth examination of the most important nodes.[6] An increase in late-stage disease detected owing to SLNB might make it seem that screening had less of an effect on decreasing late-stage disease. The increased incidence of node-positive disease detected owing to SLNB in the Danish population has been estimated to be 3.9%;[7] U.S. population data are difficult to find and interpret.[8]

The greater use of better staging investigations, such as bone scans and computed tomography scans, in more recent years might also result in more late-stage disease being diagnosed; however, this likely has had little effect because these tests are not recommended for early-stage disease and, even if ordered, the incidence of clinically occult metastatic disease in patients with early-stage breast cancer is less than 3%.[9,10] Similarly, the use of chemoprevention for breast cancer is another potential confounding factor, but likely it too would have a small effect.[11,12]

The authors also examined the validity of their assumptions around the annual incidence of breast cancer over time. For their primary analysis, the authors assumed that the incidence or disease burden was constant over time. In addition, they also analyzed the data using a "best guess" estimate, which allowed the baseline incidence to increase by 0.25% annually. This was derived from the increased incidence observed in women younger than 40 years (who were assumed not to have undergone screening) over this time frame. The best guess estimate provided somewhat more favourable reductions in the decrease in the incidence of late-stage cancers from 8 cases per 100 000 to 16 per 100 000.

There are a number of difficulties with such population-based analyses. The authors included all women older than 40 years in their analysis, despite the consistent finding that the risk:benefit ratio is less favourable in women younger than 50 years.[13–15] Furthermore, the reality is that most screening mammography in the United States is not programmatic and includes more frequent intervals than the biennial schedule used in most international programs. Annual intervals for women aged 40–69 years have been estimated to yield nearly 3 times the rate of unnecessary biopsies than biennial screening in women aged 50–69 years.[15] Over the past 20 years, programs in Canada, Great Britain and Australia have focused on women older than 50 years, generally using biennial intervals. Thus, the results of this study are likely not generalizable to other countries.

The authors conclude that despite substantial increases in the number of cases of early-stage breast cancer detected, screening mammography in the United States has only marginally reduced the rate at which women present with late-stage cancer. The imbalance suggests that there is substantial overdiagnosis, accounting for nearly one-third of all newly diagnosed breast cancers, and that screening is having, at best, only a small effect on the rate of death due to breast cancer. Effectiveness in health care is the extent to which an intervention achieves its intended purpose in real world conditions. These findings should result in some sober reflection of screening practices in the United States and other jurisdictions.

Finally, while women in the United States may be interested in the knowledge that by avoiding screening mammography they can reduce their risk of receiving a breast cancer diagnosis by one-third,[16] many women will still accept this 31% chance of overdiagnosis and the harm of "unnecessary" treatment if there is a reasonable chance that this intervention can avert breast cancer–related mortality and/or if it will reduce the likelihood of requiring more morbid breast cancer treatments. This study, unfortunately, does not settle the controversy surrounding the benefits of screening but rather adds further fuel to the ongoing debate.

Competing interests: None declared.

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